

PATENT IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF

JAMES A. SIKORSKI ET AL

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EXAMINER: RICHARD L. RAYMOND

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TITLE: (R)-CHIRAL HALOGENATED SUBSTITUTED N,N-BIS-PHENYL  
AMINOALCOHOL COMPOUNDS USEFUL FOR INHIBITING  
CHOLESTERYL ESTER TRANSFER PROTEIN ACTIVITY

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INFORMATION DISCLOSURE STATEMENT  
UNDER 37 CFR §1.97-1.99

Hon. Commissioner of Patents & Trademarks  
Alexandria, VA 22313-1450

Sir:

This Information Disclosure Statement is filed pursuant to 37 CFR §1.97-1.99, as supplemented by MPEP §609. Attached is PTO Form 1449 listing documents believed to be material to the subject matter claimed in the above-identified application as of the filing date of said application.

Presentation of these documents listed on PTO Form-1449 is not an admission that any listed document is prior art under the Patent Statutes and the right is reserved to antedate any material described in the listed documents by a showing under 37 CFR §1.131 or otherwise.

The pertinence of each of these documents is summarized below:

**Ref. AA** describes a process to produce 3-amino-2-hydroxy-1,1,1-trifluoromethyl compounds having utility as drug intermediates and in which the amino group is optionally substituted with a phthaloyl, 1 or 2 substituted- and unsubstituted-C<sub>1-30</sub> alkyl groups or 1 or 2 substituted- and unsubstituted-C<sub>6-35</sub> aryl groups. The preparation of (3S)-N,N-dibenzyl-3-amino-4-methyl-1,1,1-trifluoromethyl-2(S)-pentanol and (3S)-N,N-dibenzyl-3-amino-4-methyl-1,1,1-trifluoromethyl-2(R)-pentanol are described. A full translation of Japanese document is provided.

**Ref. AB** describes a laboratory synthesis of N,N-dibenzyl-1-amino-2-hydroxy-3,3,3-trifluoropropane compounds substituted at the 1-position by a 2-phenylethyl or cyclohexylmethyl group.

**Ref. AC** describes a laboratory synthesis of N,N-dibenzyl-1-amino-2-hydroxy-3,3,3-trifluoropropane compounds.

**Ref. AD** describes a laboratory synthesis of N-(2-amino-6H-5-nitro-6-oxo-4-pyrimidinyl)-N-benzyl-1-amino-2-hydroxy-3,3,3-trifluoropropane.

**Ref. AE** describes a laboratory synthesis of N,N-diphenyl, N-methyl-N-phenyl, and N-ethyl-N-phenyl 1-amino-2-methoxy-2,3,3,3-tetrafluoropropane and 1-amino-2,2-dimethoxy-3,3,3-tetrafluoropropane compounds. The phenyl is optionally substituted by one or more methoxy and methyl groups.

**Ref. AF** describes the laboratory conversion of dibenzylamine to N,N-dibenzyl-4-amino-1,1,1-trifluoro-2-butanol compounds as versatile synthetic intermediates to spermidines.

**Ref. AG** describes the laboratory conversion of dibenzylamine to N,N-dibenzyl-3-amino-1,1,1-trifluoro-2-propanol and the preparation of 2-benzylamino-3,3,3-trifluoropropanol and 1-(N-benzyl-N-methylamino)-3,3,3-trifluoro-2-propanol as synthetic intermediates.

**Ref. AH** describes the laboratory preparation of N,N-dibenzyl-3-amino-3-substituted-1-iodo-2-propanol compounds as synthetic intermediates.

**Ref. AI** describes the laboratory preparation of N,N-dibenzyl-3-amino-3-substituted-1-chloro-2-propanol compounds as versatile synthetic intermediates to aminoalkyl epoxides.

**Ref. AJ** describes the laboratory preparation of enantiopure N,N-dibenzyl-3-amino-3-substituted-1-chloro-2-propanol compounds as versatile synthetic intermediates to hydroxyethylamine-based HIV protease inhibitors.

**Ref. AK** describes the laboratory preparation of N,N-dibenzyl-3-amino-3-substituted-1-iodo-2-propanol compounds as versatile synthetic intermediates to regioisomeric aminiodohydrins.

**Ref. AL** describes the laboratory preparation of N,N-dibenzyl-3-amino-3-benzyl-1-chloro-2-propanol compounds as a key building block for HIV-protease inhibitors.

**Ref. AM** describes N-aryl-N-alkyl-1-amino-2-hydroxy dihalo and trihalo alkane compounds useful in promoting the growth of ruminants. The aryl group is optionally substituted with a halogen or a C<sub>1-4</sub> alkoxy.

**Ref. AN** describes N-alkyl, N-aryl and N-heterocyclyl 1-amino-2-hydroxy-3,3,3-trifluoropropane compounds useful in the preparation of dye compounds. The aryl is optionally substituted by alkyl and halo, and the amino group is optionally further substituted by alkyl, hydroxyalkyl, and cyanoalkyl.

**Ref. AO** describes fused heterocyclyl pyridine compounds having CETP inhibitory activity and with utility for treating atherosclerosis and blood-lipid disorders.

**Ref. AP** describes N-C<sub>1-6</sub> alkyl-N-(2-(disubstitutedphenyl)-ethyl)-2-aminoethanol compounds having utility as hypoglycemic and antiobesity agents. The ethane is substituted at the 2-position by phenyls, phenoxyalkyls, pyridyls, pyrimidinyls, thiazolyls and oxazolyls.

**Ref. AQ** describes N-(2-(disubstitutedphenyl)alkyl)-2-amino-1-(3-pyridyl)ethanol compounds having utility as hypoglycemic and antiobesity agents.

**Ref. AR** describes (R<sub>3</sub>-L<sub>1</sub>)-R<sub>1</sub>-R<sub>2</sub>-R<sub>4</sub>-benzene compounds, compositions thereof, and pharmaceutical utilities thereof. R<sub>3</sub> is a substituted- or unsubstituted-aryl, heteroaryl or cycloalkyl, and L<sub>1</sub> can be -L<sub>4</sub>-N(R<sub>5</sub>)-L<sub>5</sub>- where R<sub>5</sub> can be haloalkyl or optionally substituted alkoxyalkyl and where L<sub>4</sub> and L<sub>5</sub> can each be an alkylene or bond. Specific compounds disclosed include N-(4,4,4-trifluoro-butyl)-N-(3,5-difluorobenzyl) derivatives of 3-(2-methylphenyl)-3-methoxycarbonylbenzylamine, 3-(2-methylphenyl)-3-(N-(1-methoxy-carbonyl-3-methylthiopropyl)amidocarbonyl)benzylamine, and 3-(2-methylphenyl)-3-(N-(1-carboxy-3-methylthiopropyl)amidocarbonyl)-benzylamine. Specific methods of use disclosed include inhibiting protein isoprenyl transferases involved in the proliferation of cancer cells or as an aid in the prevention of intimal hyperplasia associated with restenosis and atherosclerosis.

**Ref. AS** describes N-hydrocarbon-N-phenyl- or N-substituted hydrocarbon-N-phenyl-quinazolinylmethylamine compounds, compositions thereof, and pharmaceutical utilities thereof. A saturated N-substituted hydrocarbon group preferably contains 1-3 carbons and 1-6 heteroatoms, for example, halogen, oxygen, nitrogen, or sulfur. A specific compound disclosed is diethyl N-[4-[(2-amino-1,4-dihydro-4-oxo-6-quinazolinyl)methyl](3-bromo-2-hydroxypropyl)amino)benzoyl]-(S)-glutamate. The compounds are disclosed to be useful as anti-cancer agents.

**Ref. AT** describes optionally disubstituted aromatic 1,4-oxazepinones, thiazepinones, diazepinones, and thiones, having the aromatic component fused into the oxazepine, thiazepine, or diazepine component with two commonly shared carbon atoms, a carbonyl or thionocarbonyl function adjacent to one shared atom and a short chain monohaloalkyl radical attached to the carbon atom two positions from the other shared carbon atom, as intermediates to compounds having antihistaminic and anti-allergy utility. The compound 4-benzyl-2-(2-chloroethyl)-2,3-dihydro-1,4-benzoxazin-5(4H)-one is specifically disclosed as an intermediate.

**Ref. AU** describes 4-aryl-2-monohalomethyl, optionally disubstituted in both aromatic rings, derivatives of 2,3-dihydro-4H-1,4-benzoxazine and 2,3-dihydro-4H-1,4-benzothiazine as intermediates to compounds having anti-psychotic activity. The compound 2-chloromethyl-4-phenyl-2,3-dihydro-4H-1,4-benzoxazine is specifically disclosed as an intermediate.

**Ref. AV** describes 1-aralkyl-4-haloalkyl optionally 3,3-disubstituted derivatives of 1,5-benzodiazepine as compounds having GnRH receptor antagonistic action and/or an action of improving sleep disturbances. The compound 1,3-dibenzyl-4-trifluoromethyl-1,3-dihydro-1,5-benzoxazin-2(2H)-one is specifically disclosed as such an intermediate.

**Ref. AW** describes 4-aralkyl-2-monohalomethyl, optionally disubstituted in both aromatic rings, derivatives of 2,3-dihydro-4H-1,4-benzoxazine and 2,3-dihydro-4H-1,4-pyridooxazine as intermediates to compounds having use in treating bacterial infections. The compound 4-(3-chlorobenzyl)-2-(2-chloroethyl)-2,3-dihydro-4H-1,4-benzoxazin-3-one is specifically disclosed as an intermediate.

**Ref. AX** describes the laboratory preparation of 4-aralkyl-2-haloalkyl derivatives of benzo-1,4-oxazepin-5-ones as intermediates to compounds having antihistaminic activity. The compound 4-benzyl-2-(2-chloroethyl)-2,3-dihydro-1,4-benzoxazin-5(4H)-one is specifically disclosed as such an intermediate.

**Ref. AY** describes the synthetic preparation of N-(gamma-chloro-beta-hydroxypropyl) arylamines and their reaction products. Specific intermediates prepared were 1-chloro-3-[(4-methylphenyl)phenylamino]-2-propanol and 1-[(2-aminolphenyl)-anilino]-3-chloro-2-propanol. A full translation of Russian document is provided. No pharmaceutical utility is disclosed.

**Ref. AZ** describes the synthetic preparation of 3-chloro-2-hydroxypropyl derivatives of aromatic amines and their reaction products. A specific intermediate prepared was 1-chloro-3-[(4-methylphenyl)phenylamino]-2-propanol. A full translation of Russian document is provided. No pharmaceutical utility is disclosed.

**Ref. BA** describes the synthetic preparation of N-(3-chloro-2-hydroxypropyl)-N-phenyl-2-naphthylamine and subsequent conversion. A full translation of Russian document is provided. No pharmaceutical utility is disclosed.

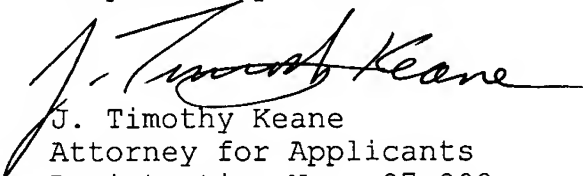
**Ref. BB** describes the synthetic preparation of N-(3-chloro-2-hydroxypropyl)-N-phenyl-1-naphthylamine and its subsequent conversion. A full translation of Russian document is provided. No pharmaceutical utility is disclosed.

Ref. BC, Ref. BD, Ref. BE, Ref. BF, Ref. BG, Ref. BH, Ref. BI, Ref. BJ, Ref. BK, Ref. BL, Ref. BM, and Ref. BN describe small molecule inhibitors of CETP which documents are less pertinent than those discussed above.

Attached is PTO Form 1449 listing documents believed to be material to the subject matter claimed in the above-identified application as of the filing date of said application. Copies of the cited documents were filed with co-pending U.S. Application Ser. No. 10/017,056 filed 12 December 2001 (Attorney Case No. SO-3182/01).

The Commissioner is authorized to charge any fee under 37 C.F.R. §1.17(i)(1) related to the filing of these documents and any additional fees to Deposit Account 19-1025.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "J. Timothy Keane", is written over the typed name.

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